Prospects of using immunotherapeutic approach in treatment of non-small-cell lung cancer patients

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Summary. In thoracic department of the National Cancer Institute studied the effectiveness of dendritic cell autovaccine in the postoperative period in non-small-cell lung cancer. The disappointing results of treatment of non-small cell lung cancer dictate the need to actively search for new approaches and areas of therapeutic intervention. Lung cancer is the leading positions on the incidence and mortality of malignant human tumors. In the world actively exploring opportunities using of combinations of chemotherapy, drugs inhibitors growth receptors, target agents, monoclonal antibodies, and biotherapeutic agents. Also great hopes are pinned on the research and development of immunotherapeutic methods, including the use of anti-cancer vaccines. The National Cancer Institute — thoracic department, together with the department of experimental oncology and department of medical physics and bioengineering, a randomized study of the efficacy of dendritic-cells autovaccine in the postoperative period in non-small cell lung cancer patients was investigated. The results obtained demonstrate the high efficiency dendritic-cells autovaccine.

Key words: lung cancer, immunotherapy, dendritic cells.

According to the National Cancer Registry of Ukraine incidence of lung cancer is 45 people per 100,000 population, the mortality rate - 38.9 people per 100,000 population, the death rate from lung cancer is 27% [4].

In the world each year more than one million patients with lung cancer. Men ill in 3 - 10 times more often than women. In 2008, there were 12.7 million cases of cancer, the first place on the statistics of men held lung cancer [1,2,3].

The two main forms are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), 15-20% of cases of SCLC and 80-85% - for NSCLC.

Surgical treatment is the primary method of treatment of patients with NSCLC. After surgical treatment of patients with stage I NSCLC, the five-year survival rate is 65 to 90%, and the median - 8 years.

American Joint Committee (AJC) for Cancer Staging and End-Results Reporting has provided the results of surgical treatment of 3912 patients with NSCLC, observed over a 6-year period in the clinic Mayo. 495 patsintov stage I were followed for more than 5 years: 84% of patients experienced a 2-year period, and 69% survived for more than 5 years. Survival of patients with T1N0M0 (stage IA) - 91% survived 2 years and 80% - 5 years [5,6].

In the world held a huge amount of clinical studies on the treatment of approaches and surgical treatment of NSCLC, stage II-IIIa in combination with chemotherapy and / or radiation exposure.

Chemotherapy is used as neoadjuvant and adjuvant setting, but the advisability of it, both before and after the operation is still in question. Researchers from the U.S. David Gilligan, Marianne Nicolson et al in 2007 provided an analysis of the results of treatment 519 patients with NSCLC using neoadjuvant chemotherapy. Patients from the first stage was 61%, the second - 31% and the third - 7%. 75% of patients received three cycles of chemotherapy, resulting in 31% of patients reported reduction stage. However, no significant increase was obtained in overall survival. Analysis of the latest data on the survival of a systematic review of 1,507 patients with NSCLC, with the inclusion of the results of the above, showed improvement of 5-year survival rate of 5% by the addition of neoadjuvant chemotherapy [7].

For years, the debate continues over the use of adjuvant chemotherapy in these patients. Although many studies have shown promising results with

postoperative chemotherapy in patients with the second stage of the disease, this treatment is not standard, therefore, the search for ways to improve the effectiveness of treatment is still actively pursued [8]

Researchers from the UK Burdett, Sarah Arriagada and colleagues analyzed the results of treatment of 8147 patients with NSCLC in 30 randomized clinical trials. We evaluated the relative effectiveness of a purely surgical treatment and surgery with adjuvant chemotherapy in patients with resectable stage: I-IIIa. Average follow-up was 5.3 years. The results obtained improve the 5-year survival rate of 4% - from 60% to 64% [9].

French researchers Jean-Pierre Le Pechoux, Cecile Tierney et al have provided a meta-analysis of 11 randomized clinical trials for the treatment of 2,626 patients II-stage IIIa NSCLC and compared the effectiveness of chemo-therapy in the adjuvant and radiation therapy postoperatively. 12% of patients with stage IIIB included in the meta-analysis suffered palliative surgery. The average follow-up period of 6.3 years. Adding chemotherapy postoperatively increased 5-year survival from 29% to 34%. Thus, the results of 41 randomized clinical trial for the treatment of over 10,000 patients with NSCLC demonstrated a benefit of adjuvant chemotherapy [10].

Currently there is no standard method that could be recommended for the treatment of NSCLC patients in the postoperative period. In stage II, undergoing a five-year observation period 41% of patients with stage IIIA, which is seen in 30-40% of the operated patients, five-year survival rate is typically less than 15%. The five-year survival rate of the entire population of patients with NSCLC in different countries is between 9 and 13% [11].

In recent decades there has been some success in the treatment of malignant tumors, primarily due to the progress of drug therapy. In addition, advances in molecular biology, immunology, in-depth understanding of the mechanisms of tumor progression and the relationship of the tumor and the immune system, as well as the development of biotechnology, have caused

real prospects for improving the results of treatment of tumors using the methods of immunotherapy. One of the promising areas, which is associated with significant prospects for improving treatment is anti-tumor vaccine therapy. The mechanism of action of antitumor vaccines, in general, similar to those of the vaccines used for prevention or treatment of infections and as it is based on the formation or transfer of a specific immune response to antigen [12,13,14,15].

Polish scientists Vansteenkiste J., Zielinksi M., et al investigated the activity immunoperparata MAGE-A3 in the treatment of IB / II NSCLC as adjuvant therapy. It was conducted a multicenter, double-blind, randomized, placebo controlled phase II study of MAGE-A3. MAGE-A3 is a recombinant protein that has demonstrated good tolerability and improved survival in the treatment of metastatic melanoma. 1089 were studied tumor samples, 363 of which showed expression of a gene MAGE-A3. 182 patients (122 - IB stage, 60 - II degree) of the 59 centers of 14 European countries were randomized for 2 years. Tumor-associated antigen MAGE-A3 is expressed in 35% of cases of NSCLC cells, and is a poor prognostic factor. The research results of the 1st and 2nd phase demonstrated the ability to influence by means of CD4 T lymphocytes in the MAGE-A3 antigen. In this study, patients who had undergone radical removal of the tumor stage IB or II NSCLC were randomized into groups - one of which was appointed by intramuscular postoperatively MAGE-A3, in the other - a placebo. Patients received 5

Immunotherapy cycles every 3 weeks, and then further injections with an interval of 83 months.

During the observation period is 28 months - at 67 patients (37%) identified relapses. In the group with MAGE-A3 relapse was on average 7% lower. In general, treatment was well tolerated. The final results provided by the researchers, showed an improvement in disease-free survival in the study group by 27% [16].

Canadian researchers Butts C., Maksymiuk A., et al have provided the results of a multicenter randomized phase II study of liposomal vaccine BLP25/Stimuvax for active specific immunotherapy of NSCLC. The mechanism of action of the vaccine is based on the effects on protein MUC 1. Mucin 1 (MUC1) is a transmembrane protein that is expressed on epithelial cells. MUC1 function is uncertain, it is believed that high tumor tissue eksperessiya this protein correlates with a reduction in apoptosis, immune suppression, and resistance to the chemotherapeutic effects and poor prognosis. MUC1 overexpressed in tumors compared to normal tissue, making it a potential target for vaccine BLP25/Stimuvax. Preclinical studies demonstrated that the vaccine may induce antigen-specific responses of T-cell proliferation and secretion of interferon-γ [17,18,19].

171 patients with IIIB / IV NSCLC after chemotherapy received BLP25 or symptomatic therapy. Patients in the group with BLP25 received a single dose of 300 mg / sqm. cyclophosphamide to reduce the activity of T-suppressors, and then began an eight-week course of vaccine therapy. 65 stage IIIB patients were followed up for 3 years. Median survival was 30.6 months for vaccinated patients versus 13.3 months in patients with symptomatic therapy. Thus, the vaccine group was higher than the median survival of 17.3 months. Demonstrated a reduction in mortality in the group with BLP25 by 45%. Marked more modest results in the analysis of survival in patients with stage IV NSCLC. The average follow-up period all patients - 53 months [20,21,22,23].

Researchers from the U.S. Giaccone G., Debruyne., Conducted a study on the effectiveness of the drug BEC2-idiotype antibodies that are similar in structure to the antigen GD3 and used in conjunction with the BCG vaccine.

GD3 ganglioside antigen is a cell surface. Gangliosides are involved in intercellular recognition, cell-matrix adhesion and cell differentiation. Preparation BEC2 is idiotypic antibodies that mimic GD3. Efficiency BEC2

was evaluated in patients with small cell lung cancer (SCLC). BCG vaccine is administered as an adjuvant to optimize immunological response. The results of a small pilot study in which patients have achieved prolonged remission of SCLC after vaccination, the impetus for the implementation of a large international Phase 3 study, which was involved in 515 patients with localized forms of SCLC after chemoradiotherapy. Toxicity was minimal, but, unfortunately, improved disease-free survival was noted. Survival of patients who have marked laboratory expression antibody response was higher, but the difference was not statistically significant.

GD3 detected in SCLC cells (and not characteristic of cells NSCLC) in about two-thirds of cases. Scientists have not determined the expression of this antigen in patients in this study, perhaps it is not possible to achieve a statistically significant increase in survival. It is suggested that patients with marked expression of GD3 in tumor tissue could get a greater benefit from the vaccine. [24]

Neninger E, Diaz RM, de la Torre A, et al. idiotype vaccine studied 1E10, which simulates its structure Neu-glycosylated gangliosides NeuGc-GM3. NeuGc-GM3 ganglioside is acetylated sialic acid, which is determined almost exclusively of transformed cells making 1E10 (NeuGc-GM3) potentially important therapeutic targeted agent. Idiotypic antibody 1E10 was investigated in preclinical models and showed antitumor activity. The second phase of clinical trials 1E10 provodolilas patients with SCLC

IIIB / IV NSCLC. Subcutaneous injections were administered once every two weeks, a total of six times, and then monthly. The preliminary report of survival of 38 patients with an average follow-up of 19 months, median survival in the vaccine group was 12.94 months versus 6 months in the control group. However, the final results are not yet available. Reported on the design of the study the third phase of 1E10 vaccine in patients with advanced NSCLC [25,26].

Leichman G, Gravenor D, Woytowitz D, et al. investigated Toll-like receptor 9 and drug PF-3512676. Toll-like receptors (TLR) represent a group of receptors that regulate antigen-specific immunity. TLR9 expressed on the surface of B-and T-lymphocytes, plasma cells and dendritic cells. TLR9 activation can reduce the severity of immunological tolerance and improve recognition of tumor antigens, which leads to cell death. Agonist activity TLR9 - PF-3512676, has been evaluated in the treatment of cancers, including NSCLC. A randomized phase 2 study for the Study of PF-3512676 in 112 patients with IIIB / IV NSCLC chemotherapy consisted in carrying out the scheme carboplatin and paclitaxel followed by subcutaneous vaccination drug PF-3512676 for 8 and day 15. Showed a trend to improved survival in a vaccine. After that was initiated Phase 3 trials PF-3512676 in patients with IIIB / IV NSCLC. After a preliminary analysis of the independent Data Monitoring Committee, the tests were terminated due to the fact that there was no statistically significant benefit in terms of survival when using PF-3512676 versus standard polychemotherapy cisplatin in combination with a taxane / gemcitabine / vinorelbine [27 , 28,29].

Also of interest is the possible use of vaccines of whole tumor cells. The vaccines of whole tumor cells have the advantage that the immune system are a complete set of tumor antigens, both known and unknown. Most of autologous and allogeneic tumor vaccine has been evaluated in patients with NSCLC. Creating autologous vaccines have certain limitations and technical problems have been necessary to obtain the antigen from the tissue of the individual patient, which is not always feasible, usually in connection with inoperable patients. The allogeneic vaccine using lung cancer cell lines, do not have such logistical difficulties, although these tumor antigens may not always be sufficient for a specific immune response. For optimal stimulation of the immune system, vaccines have been developed on the basis of genetically modified tumor cells that cause release of cytokines and

immunosuppressive proteins. Such type vaccines include: granulocyte macrophage colony stimulating factor (GM-CSF)-immunized cancer cells (Granulocyte-Macrophage Colony-Stimulating Factor-Transduced Allogeneic Cancer Cellular Immunotherapy; GVAX; Cell Genesys Inc) and drug Belagenpumatucel-L (Lucanix; NovaRx Corporation) [30].

Nemunaitis J, Jahan T, Ross H, et al. reported the 1st and 2nd stage research GM-CSF-vaccine called GVAX. In the first phase, the vaccine was used in 37 patients with NSCLC. GVAX vaccination was well tolerated, have been reported remission lasting longer than 40 months.

In the second phase of the research GVAX was used in 43 patients with NSCLC (33 patients with relapsed disease) [31,32]. GVAX was administered every 2 weeks for a total of 3 to 6 shots. The toxicity profile was satisfactory, 3 patients with stage IV NSCLC achieved long-term remission in 2 cases, which reached almost 5 years.

It should be noted that in this study the attempt made GVAX treatment in 83 patients with NSCLC, but due to technical difficulties, only 43 patients were vaccinated. In 16 cases the vaccine could not be made due to lack of tumor tissue, especially when the source of tumor cells was used pleural fluid. In addition, the vaccine production time is 49 days, which is not always acceptable in patients with advanced forms of the disease.

Interestingly message Salgia, Lynch et al., About three out of four patients with bronchioloalveolar carcinoma who achieved long-term remission. It is assumed that bronchioloalveolar cancer can be of viral origin, and in this regard immunotherapy may be particularly promising for this histological subtype of NSCLC. Currently, GVAX evaluated in a phase 2 trial in patients with IIIB / IV stage bronchioloalveolar cancer, in order to investigate this matter. [33]

Transforming growth factor-β2 antisense gene-modified allogeneic vaccine opuholevokletochnaya (Transforming Growth Factor β2 Antisense

Gene-Modified Allogeneic Tumor Cell Vaccine): Belagenpumatucel-L (Lucanix; NovaRx Corporation) developed from allogeneic NSCLC cell lines that are genetically modified that emit antisense oligonucleotides to transforming growth factor-β2 (TGF-β2). TGF-β2 is an immunosuppressive drug that suppresses the activity of natural killer cells, activated killer cells and dendritic cells. TGF-β2 has been identified as one of the adverse prognostic factors of NSCLC. Preclinical studies indicate that inhibition of TGF-β2 enhances the immunogenicity of tumor vaccines. Unlike GVAX, in the manufacture belagenpumatucel-L using allogeneic tumor cell line and there is no requirement to obtain a particular tumor tissue for each patient. Also, do not require long cooking time vaccine. A randomized phase 2 trial in 75 patients with II, III, IV stage NSCLC, after the completion of standard chemotherapy. Toxicity was negligible. Received 16% of the responses to the vaccine. Patients who received low doses of the vaccine were inferior in terms of survival to other groups with higher doses. Median survival for patients receiving 25 million and 50 million cells per injection was 581 days, as compared to 252 days for patients receiving 12.5 million cells per injection. Biological markers of immune stimulation, including cytokine production by mononuclear cells and the development of an immune response to the vaccine, the results correlated with the best survival, although not significantly and statistically. Belagenpumatucel-L is currently in phase 3 clinical trials [34].

In addition to these drugs are already registered a number of targeted therapies shown to be effective in the treatment of NSCLC: bevatsuzimab, cetuximab, erlotinib, Iressa.

In the past two decades, considerable attention has been the inclusion of the anti-vaccine antigen-presenting dendritic cells (DC).

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